

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS

1. (*currently amended*): A method of treating a deficiency of a Hedgehog protein in the gastrointestinal (GI) tract of an adult subject who has a deficiency ~~deficient~~ in said protein and is in need of such treatment, comprising providing to the GI tract of the subject in need thereof a composition that comprises a source of a Hedgehog protein, selected from the group consisting ~~source of:~~

- (a) a polypeptide comprising an amino acid sequence with at least 63% sequence identity to SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3;
- (b) a nucleic acid expression vector comprising a nucleotide sequence that encodes the polypeptide of (a) and which is expressed in the subject;
- (c) a bacterial delivery vehicle comprising a non-pathogenic enteric bacterium, capable of colonizing the subject's GI tract, which bacterium is transformed with said expression vector of (b) and expresses and secretes said polypeptide of (a); and
- (d) an animal cell that expresses and secretes said polypeptide of (a);

wherein the polypeptide of (a) has at least one of the following biological activities:

- (i) binds to Hedgehog binding receptor Patched;
- (ii) maintains homeostasis of adult intestinal epithelium;
- (iii) restores epithelial differentiation of GI tract cells, avoiding carcinogenesis; and/or
- (iv) causes GI epithelial tumorigenic cells to undergo a cell death program, avoiding carcinogenesis and allowing shedding of these cells into the GI lumen.

2. (*currently amended*): A method according to claim 1 [[30]], wherein the ~~subject is at risk for, or suffers from cancer of the GI tract and said providing of said composition~~ results in

- (i) prevention of development of said cancer of the small intestine or colon ~~development~~, or
- (ii) therapy of said cancer of the small intestine or colon.

3. (*currently amended*): A method according to claim 2, for the therapy of ~~wherein the cancer is gastric or~~ small intestine or colon cancer.

4. (*currently amended*): A method according to claim 2, wherein the cancer is a ~~GI tract~~ carcinoma and ~~said~~ providing of said composition results in therapy of said carcinoma.

5. Cancelled

6. (*previously presented*): A method according to claim 1, wherein the deficiency of the Hedgehog protein is an acquired deficiency.

7. (*currently amended*): A method according to claim 1[[30]] wherein the subject has familial adenomatous polyposis coli (FAP).

8. (*currently amended*): A method according to claim 7, wherein the source of the Hedgehog protein, ~~homologue or variant, nucleic acid expression vector, bacterial delivery vehicle, animal cell or inducing or upregulating agent,~~ is administered in an amount effective to ~~reverse prevent or treat small intestine or colon~~ GI tract tumorigenesis in the FAP subject[[]].

9. (*currently amended*): A method according to claim 7, wherein the source of the Hedgehog protein, ~~homologue or variant, nucleic acid expression vector, bacterial delivery vehicle, animal cell or inducing or upregulating agent,~~ is administered in an amount effective to prevent or treat ~~reverse~~ colonic adenomatous polyps, invasive adenocarcinomas, small intestinal adenomas and cancers, ~~or and~~ desmoid tumors.

10. (*currently amended*): A method according to claim 1[[30]] wherein the source of Hedgehog protein is a pharmaceutical composition comprising ~~comprises the~~ polypeptide of (a) ~~Hedgehog protein, homologue or variant in a pharmaceutical composition.~~

11. (*original*): A method according to claim 10, wherein the pharmaceutical composition is suitable for oral administration.

12. (*currently amended*): A method according to claim 1[[30]], wherein the source of the Hedgehog protein is a pharmaceutical composition comprising ~~comprises~~ said nucleic acid vector of (b) in a pharmaceutical composition.

13. (*currently amended*): A method according to claim 1[[30]], wherein the source of Hedgehog protein comprises said enteric bacterium of (c).

14 – 24: (Cancelled)

25. *(withdrawn)*: A method for determining whether a subject is at risk for developing a GI tract tumor comprising measuring the level of a Hedgehog protein or a Hedgehog mRNA in a GI tract tissue sample from the subject.

26. *(withdrawn)*: A method according to claim 25, wherein the tissue sample is gastric, esophageal or colon tissue.

27. *(withdrawn)*: A method for diagnosing (i) the susceptibility of a subject to develop , or (ii) the presence in a subject of, ectopic gastric tissue comprising determining the level of Hedgehog, BMP2 or BMP4 mRNA and/or protein in a tissue sample from the subject.

28. *(withdrawn)* A therapeutic composition comprising a nucleotide sequence encoding a Hedgehog protein which composition is in the form of.

- (a) a nucleic acid expression vector; or
- (b) an enteric bacterium comprising the nucleotide sequence which bacterium is capable of secreting the Hedgehog protein when colonizing the GI system of a subject.

29. *(withdrawn)*:The therapeutic composition of claim 28 which is said enteric bacterium .

30. Cancelled

31. *(currently amended)*: The method of claim 1[[30]] wherein said Hedgehog protein is Sonic Hedgehog [[Shh]] or Indian Hedgehog ~~Ihh~~ and said homologue or variant is a homologue or variant of Shh or Ihh.

32. *(withdrawn)*: A method for preventing the development or treating a disease or condition characterized by the presence or growth of a Hedgehog protein-expressing ectopic gastric tissue in a subject, comprising providing to the subject or to the site of said ectopic tissue an effective amount of a substance that reduces the functional level or activity of the Hedgehog protein.

33. *(withdrawn)*: A method according to claim 32, wherein said substance is an antibody specific for said Hedgehog protein or an antisense nucleic acid at least part of which is complementary to at least a functional part of a Hedgehog mRNA that encodes a Hedgehog protein selected from the group consisting of human Desert Hedgehog protein SEQ ID NO:1, human Indian Hedgehog protein SEQ ID NO:2, and human Sonic Hedgehog protein SEQ ID NO:3.

34. *(new)* A method according to claim 1 wherein the polypeptide that has the activity of binding to a Hedgehog binding receptor Patched, activates signaling downstream of Patched through a receptor Smoothened and transcriptional effects of a Gli transcriptional effector family member.
35. *(new)* A method according to claim 1 wherein the polypeptide of (a) comprises an amino acid sequence with at least 75% sequence identity to SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3.
36. *(new)* A method according to claim 35 wherein the polypeptide of (a) comprises an amino acid sequence with at least 80% sequence identity to SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3.
37. *(new)* A method according to claim 36 wherein the polypeptide of (a) comprises an amino acid sequence with at least 90% sequence identity to SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3.
38. *(new)* A method according to claim 37 wherein the polypeptide of (a) comprises an amino acid sequence with at least 95% sequence identity to SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3.